REMARKS

The outstanding Office Action is responsive to Applicants' amendment filed August 23, 2006. However, a Supplemental Amendment filed with the Office on December 22, 2006 containing certain amendments to the claims was, apparently, not entered or considered. Applicants believe that the amendments and remarks made in the Supplemental Amendment address certain issues in the outstanding Office Action. Since the Supplemental Amendment was not entered, the claims section of the present amendment reflects the changes made to the claims as of entry of Applicants' amendment filed August 23, 2006. Applicants request entry and consideration of the present amendment and remarks.

By the present amendment, claims 5-7 and 14 have been canceled without prejudice, and claim 29 has been amended. Accordingly, claims 2-4, 10-13, 15-24, 29, and 32-39 are pending in the application, with claims 17-24 and 32-39 standing withdrawn from consideration. Applicants have amended claim 29 for purposes of clarity to more particularly claim the intradermal delivery of insulin. Claim 29 as amended recites that the insulin is delivered through the lumen of the needle into the intradermal compartment and distributed systemically exhibiting a higher maximum plasma concentration and a higher bioavailability as compared to subcutaneous delivery. Applicants have amended the claims to expedite prosecution and allowance of the application. The amended claims are fully supported by the instant application, and no new matter has been added. Support for the amendment to claim 29 can be found, for example at page 4, lines 1-2 in combination with page 6, lines 2-6, and Figure 4.

The Claim Objection under 37 CFR 1.75(c) Has Been Rendered Moot

Claim 14 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In response, Applicants have canceled claim 14, thereby rendering the basis for the rejection moot. Applicants respectfully request withdrawal of the objection.

The Rejection of Claims 2-5, 10-16, and 29 under 35 U.S.C. § 112, First Paragraph as Failing to Comply with the Enablement Requirement Should Be Withdrawn

Claims 29, 2-5 and 10-16 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not reasonably provide enablement for ID delivery of all drugs.

Without conceding to the propriety of the rejection, and solely to expedite prosecution of the present application, Applicants submit that the amended claims directed to intradermal delivery of insulin are fully enabled by the instant specification. As the Examiner has indicated in the Office Action mailed January 4, 2007, the specification is enabling for delivery of insulin to the intradermal compartment of the skin. The amendment has thereby rendered the asserted grounds for the rejection moot.

Applicants request reconsideration and withdrawal of the rejection for lack of enablement in view of the amended claims.

The Rejection of Claims 2-7, 10-16, and 29 under 35 U.S.C. § 112, Second Paragraph Has Been Rendered Moot

Claims 29, 2-7 and 10-16 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. According to the Examiner, claim 29 recites that the pharmacokinetic profile between ID and SC injections is similar, but contends that the specification fails to clarify the similarities in ID and SC delivery methods, while at the same time showing a higher C_{max} and higher bioavailability.

Without conceding to the propriety of the rejection, and solely to expedite prosecution of the present application, Applicants have amended claim 29 to recite that the insulin is delivered through the lumen of the needle into the intradermal compartment and distributed systemically exhibiting a higher maximum plasma concentration and a higher bioavailability as compared to subcutaneous delivery. Accordingly, the amendments to the claims render the grounds for the rejection moot. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, in view of the amended claims.

The Rejection of Claims 2-7, 10-16, and 29 under 35 U.S.C. § 103, Should Be Withdrawn

Claims 29, 2-7 and 10-16 are rejected under 35 U.S.C. §103(a) as obvious over Gross *et al.* (U.S. Patent No. 5,848,991, "Gross I") or Gross *et al.* (U.S. Patent No. 5,807,375,

"Gross II") in view of Prausnitz (U.S. Patent No. 6,611,707), Autret, Puri, D'Antonio *et al.* (U.S. Patent No. 6,056,716), Srivastava (U.S. Patent No. 6,007,821, "Prausnitz"), and The Merck Manual of Diagnosis and Therapy (17th ed.)(1999). The Examiner contends that to the extent that Gross is silent with respect to needle outlet exposed height and the pharmacokinetic profile of the ID delivered drug - - the missing elements are supplied by Prausnitz, Autret, Puri, D'Antonio, Srivastava and Merck.

The instant claims have been amended to recite a method of administrating insulin to the intradermal compartment comprising:

(a) administering via a needle to the intradermal compartment so that the needle's outlet depth and exposed height are within the intradermal compartment and wherein the outlet has an exposed height of about 0 to about 1 mm;

(b) delivering the insulin through the needle with the application of pressure to control the rate of delivery;

(c) so that when insulin is delivered it has a higher bioavailability and a higher plasma concentration as compared to subcutaneous administration.

The Examiner is relying on the combination of Gross and Prausnitz to provide the suggestion of claim elements (a) and (b); and is relying on Autret, Puri, D'Antonio, Srivastava and Merck Manual to provide the suggestion of claim element (c). However, the cited references are completely silent as to the needle configuration and needle placement as required by claim elements (a) and (b). The cited references are equally silent as to the improved pharmacokinetics resulting from intradermal administration as claimed. Finally, the claims have been amended to recite the administration of insulin, and none of the cited references describe improved pharmacokinetics of insulin when delivered intradermally. Thus, for the reasons discussed below, the cited references do not render obvious the claimed invention.

First, Gross does not describe the insertion of a needle so that *both* its outlet depth and exposed height of the outlet are located within the intradermal compartment of the subject's skin. Further, Gross does not describe a needle having an outlet with an exposed height of about 0 to 1 mm. These elements of the claims are not taught or suggested by Gross. Instead, Gross proposes methods and devices that *non-selectively* administer drugs below the epidermis, *i.e.*, to the interface between the epidermis and the dermis, or to the interior of the dermis or subcutaneously (*see* Gross at col. 3, *ll.* 38-45). In addition, not only is Gross silent

as to the claimed pharmacokinetic profile, practicing Gross does not inevitably result in the claimed profile.

Indeed, practice of the claimed method of intradermal delivery has a very different outcome as compared to delivery in accordance with Gross as demonstrated by the concurrently filed Third Declaration under § 1.132 of Dr. Ronald J. Pettis ("Declaration"). The Declaration demonstrates that delivery in accordance with the claimed configuration has a dramatic effect on the results obtained when compared to the results reported by Gross. Namely, administration in accordance with the claimed configuration dramatically affects the resulting pharmacodynamic profile, including both the rate and magnitude of the drop in blood glucose concentration as compared to Gross. *See*, Declaration.

As reported in Example 1 of Gross, when insulin was administered "intradermally" to rabbits, the rabbits' glucose levels dropped, and rose again when insulin administration ceased. However, rabbits receiving insulin in accordance with the claimed method demonstrated a much more precipitous drop in blood glucose concentrations. *See*, Declaration at ¶ 15 and Exhibits B, C, D, and E. In fact, as a result of intradermal administration of insulin in accordance via the claimed method at 100 IU/mL, the blood glucose concentrations of the test animals dropped to levels which could not be reversed by ceasing administration of insulin, nor by intervening through administration of glucose to the hypoglycemic test animals. This result indicates that there apparently was a high maximum plasma concentration and bioavailability of insulin when it was administered via the claimed method; hence the same hypoglycemic shock experienced by the test animals, as opposed to the result obtained by the methodology described in Gross, where the animals easily recovered once insulin administration ceased. Had Gross been practicing intradermal delivery as claimed in the instant application, the same result would have been observed; it was not. *See*, Declaration at ¶ 8.

One possible explanation for the differences in the observed pharmacodynamic response is that Gross fails to define the intradermal compartment, but merely describes delivery below the epidermal layer of the skin. Gross is devoid of any teaching relating to the configuration of the needle required to prevent leakage of the drug substance outside the intradermal space. It is the Applicants' disclosure, not Gross, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at p. 5, *l.* 19-p. 6, *l.* 15). Unless the skin seals around the needle, the drug

substance will effuse out of the skin due to backpressure exerted by the skin itself, or the pressure built up from the accumulating fluid. The Applicants' specification sets forth principles and parameters relating to length of the needle and configuration of its outlet to prevent unwanted leakage. The Applicants' teachings also address mechanisms that can be used to provide adequate pressure so that the drug is efficiently and consistently delivered to the intradermal compartment of human skin where it is readily absorbed and systemically distributed. (For proper needle length and outlet configuration, *see*, instant specification at p. 5, *l.* 19-p. 6, *l.* 15; for proper pressure requirements to achieve intradermal delivery *see*, instant specification at p. 6, *l.* 16-p. 7, *l.* 4). In particular, the specification describes the use of microneedles that have *both* a length sufficient to penetrate the intradermal space *and* an *outlet depth within the penetration space* to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure *(see*, specification at p. 5, *l.* 33-p. 6, *l.* 3). Gross neither appreciates nor addresses the significance of these parameters for practicing the claimed method.

Contrary to the Examiner's position, these missing parameters from Gross are not provided by Prausnitz. Prausnitz describes a microneedle device for delivery across or into skin. However, for transdermal applications the "insertion depth" of the needle is preferably less than 100-150 μm, so that insertion does not even penetrate into the intradermal compartment (*see*, Prausnitz at col. 4, ll. 7-11). While Prausnitz does describe needles having overall lengths longer than 150 μm, Prausnitz specifically recites that the overall length of the needle is *not* equal to the inserted length. According to Prausnitz, the distal tip of the needle is *not* inserted into the skin and the actual length of the uninserted portion depends on the device design and configuration. (*see*, Prausnitz at col. 4, ll. 11-17). Thus, Prausnitz fails to describe a needle configured so that *both* its outlet depth and exposed height of the outlet are located within the intradermal compartment of the subject's skin.

The remaining references cited by the Examiner fail to describe or suggest the claimed needle configuration, and further fail to describe or suggest the claimed pharmacokinetic profile. In addition, given that the claims have been amended to cover administration of insulin, a number of the references cited by the Examiner are no longer relevant to the patentability of the pending claims.

For example, Autret is concerned with delivery of calcitonin, not insulin. Further, Autret concludes that the plasma levels of calcitonin resulting from intradermal and subcutaneous administration are *not different* (*see*, Autret, Summary at p. 5). Contrary to the

Examiner's assertion, Autret does *not* describe enhanced plasma levels resulting from intradermal delivery. As concluded by the authors of Autret, there is no difference in plasma levels of calcitonin when intradermal and subcutaneous delivery are compared.

Puri, D'Antonio and Srivastava are concerned with vaccine delivery - - not the delivery of insulin. The efficacy of a vaccine is measured by the ability of the body to mount an antibody response to the vaccine. Methods of assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not injected vaccine) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system.

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as practitioners in this field do not gauge the potency of a vaccine by its ability to be circulated systemically. Thus, Puri, D'Antonio and Srivastava do not describe, nor do they suggest an enhanced bioavailability or plasma levels of insulin as required by the claims.

In sum, none of the references taken alone or in combination describe or suggest administration via a needle having the claimed configuration and placement in the intradermal compartment. The references taken alone or in combination are equally silent as to the improved pharmacokinetic profile – enhanced plasma levels and bioavailability of insulin when delivered intradermally. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Provisional Double Patenting Rejections Should Be Held In Abeyance

Claims 2-7, 10-16, and 29 are provisionally rejected on the non-statutory ground of obviousness-type double patenting over claims 8 and 10 of copending Application No. 10/868,482; claims 1, 2, 7, 8, and 50 of copending Application No. 10/867,908; claims 1-7, 9, 13, 16, 26, 28-30, 32, 35-41, 46-48, 50, 52-54, 57, 59, and 62-64 of copending Application No. 10/487,485; claim 25 of copending Application No. 11/004,780; claim 25 of copending Application No. 11/004,778; claims 1-3, 8, 10-16 of copending Application No. 10/841,992; claims 66 and 76 of copending Application No. 10/803,735; claims 22-26, 29-31, and 33 of copending Application No. 10/650,039; claim 33 of copending Appl. No. 10/249,973; claims 65, 71, 72, 75-77, and 82 of copending Application No. 09/893,746; claims 31, 32, 36, 37,

39, 49, 67, and 73 of copending Application No. 10/028,988; and claims 69, 72, 83-86, 88, 90, 100, and 103 of copending Application No. 10/028,989 in view of Gross '991 or Gross '375, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava. As this is provisional obviousness-type double patenting rejection, Applicants respectfully request that the rejection be held in abeyance until such time as the Examiner indicates there is allowable subject matter, at which time the matter will be revisited in light of the allowable subject matter. Applicants respectfully submit that they will consider filing Terminal Disclaimers at which time allowable subject matter is identified. Based on the ability to file Terminal Disclaimers for each of the co-pending applications above and the statement filed above, Applicants respectfully request that the provisional double patenting rejections of claim 2-7, 10-16, and 29 be withdrawn and that claims 2-7, 10-16, and 29 be allowed.

CONCLUSION

Applicants respectfully request that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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Respectfully submitted, /: Eric A. Meade Reg No. 42,876

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